and include a 24 residue limitation on the sensor peptide in all the independent claims, and a 12 residue limitation on the sensor peptide in new claim 31. Support for the 24 and 12 residue limitations is found on p.4, line 31. These amendments introduce no new matter.

The pending claims are identical to those in the counterpart PCT application No. PCT/US98/24969. The following comments are responsive to the inventive step issue raised in the Written Opinion dated 12 JAN 2000 in the counterpart PCT application in view of Baylor (WO97/10337).

Baylor describes the cloning of SRC-1, a progesterone receptor (PR) coactivator. SRC-1 ensures ligand-dependent activity of the steroid receptor by interacting with the ligand binding domain of the receptor in a hormone specific manner. The cited portions of Baylor describe SRC-1 by sequence and contemplate functional deletion mutants (p.7-8), a use of SRC-1 transgenes coupled to a "gene switch" whereby ligand activates both the SRC-1 and target gene (p.16-18), SRC-1 derivatives (p.69) and fragments (p.73), a PR-based yeast two-hybrid screening system (p.83-84), a method for making hPR-coupled affinity beads (p.84-85) and transiently transfecting cells with a SRC-1 gene and assaying for reporter CAT activity (p.88-89), use of the progesterone receptor-based yeast two-hybrid system to isolate SRC-1 (p.89-91), and use of the affinity beads to show ligand dependent binding of SRC-1 to progesterone receptor (p.91-92).

Baylor's discussion of SRC-1 fragments is entirely speculative and generic: "25 (preferably 30, more preferably 35, most preferably 40) or more contiguous amino acids ... polypeptides of 50, 10, 425, 430, 440 or more amino acids are preferred ... the amino acid sequence is preferably substantially similar to the sequence shown in Figure 1, or fragments thereof" (p.7, line 23 - p.8, line15). The application discloses several exemplary, non-limiting functionalities relating to receptor binding, transactivation, etc. (p.8, lines 4-13). Hence, the application purports to encompass any protein containing any functional peptide having substantial sequence similarity to any fragment of the disclosed SRC-1. In fact, the only functional deletion mutants disclosed in Baylor are that encoded by SRC-1(.8) which is 800bp in length (p.93, line 4) and a receptor binding domain of residues 865-1061 (p.100, line 22), which is 197 amino acids in length.

All the pending claims require an in vitro mixture comprising a nuclear hormone receptor, a peptide sensor and a candidate agent, but not a natural coactivator protein of the first receptor, wherein the sensor provides direct, agonist-dependent assay detectable binding to the receptor and comprises 24 or fewer amino acids. The issue is whether Baylor suggests such mixture, and specifically comprising such a sensor.

One of ordinary skill in the art at the time of our filing date would not have expected such small peptides to provide direct, agonist-dependent assay detectable binding to the receptor. At best, one of ordinary skill may have speculated that full and intact structurally defined folding domains (SH2 domains, leucine zippers, SH3 domains, pleckstrin homology domains, PTB domains, etc) *might* be sufficient to provide certain functionality. Such speculation would be supported by Baylor's evidence of a 197 residue functional domain. However, such speculation is a far cry from suggesting that smaller peptides of 24 or fewer or of 12 or fewer residues could retain such functionality. That such small peptides could provide agonist-dependent binding was entirely unexpected because they are smaller than that believed required to form typical structurally defined folding domains. For good measure, Applicants append a Declaration of a renowned expert in the field of transcriptional regulation demonstrating the foregoing, that one of ordinary skill in the art at the time the invention was made, would have found the invention - requiring a peptide sensor which provides direct, agonist-dependent assay detectable binding to the receptor and comprises 24 or fewer amino acids - nonobvious in view of the Baylor reference.

Respectfully submitted,
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